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A Highly Enantioselective Intramolecular Heck Reaction with a Monodentate Ligand

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Since the first reports in the late 1980s[1] the asymmetric Heck reaction (AHR) has received considerable attention.[2−4] High selectivities have been reached by using bidentate ligands, usually phosphines (predominantly BINAP) or phosphine-oxazolines. A number of intermolecular AHR's with ee's >96% have been reported.[2,3] For the intramolecular AHR, however, the ee values are typically around 80% with notable exceptions leading to ≥90% ee.[5] The intramolecular AHR has featured a prominent role in the synthesis of complex natural products.[2,3,5]

We have shown that phosphoramidites are versatile ligands for a variety of catalytic asymmetric transformations.[6] Despite the fact that the classic Heck reaction was shown to occur in the presence of phosphoramidites,[7] the use of phosphoramidites as chiral ligands in an AHR resulted in very low enantioselectivity.[8]

We designed prochiral cyclohexadienone **1** as a new substrate for the intramolecular AHR (see Figure 1).[9] Upon AHR, the stereogenic center is not created at the site of C−C bond formation, but instead the cyclohexadienone is desymmetrized. We expected the chiral catalyst to show high face-selectivity (based on the excellent face-selectivity already observed in asymmetric 1,4-additions to cyclohexadienones[10]) leading to 4a-methoxy-4a*H*-benzo[*c*]chromen-2(6*H*)-one, which could act as a model compound for, e.g., the synthesis of the anticancer *Amaryllidaceae* alkaloid pancratistatin.[11]

Herein we report cyclohexadienones as new substrates for the intramolecular AHR and the remarkable finding that monodentate phosphoramidites are effective ligands for this highly enantioselective AHR with ee's up to 96%.

Cyclohexadienone **1** is efficiently synthesized in two steps from commercially available 2-iodobenzyl chloride **3**. Formation of the monoether of hydroquinone in 91%, using benzyl chloride **3**, is followed by phenolic oxidation with phenyliododiacetate (PIDA) in MeOH[12] to provide **1** in 83% yield. (Scheme 1)

Since, to the best of our knowledge, all successful ligands used so far for the AHR were bidentate, we focused our initial studies on the use of bidentate TADDOL-based phosphoramidite **L*-1** as chiral ligand.[13] Employing an in situ prepared catalyst from $Pd(OAc)_2$, and **L*-1** (1:2 ratio) in the presence of K_2CO_3 as a base in THF we indeed obtained with full conversion of the starting material product **2** in 68% ee[14] (Table 1). Changing the solvent to $CHCl_3$ resulted in full conversion and 86% ee. For NMP and DMA, commonly used solvents in Heck couplings, the stereoselectivities were much lower (ee <60%), whereas for acetonitrile and DMSO racemic product was obtained due to a very fast background reaction (not involving **L***).

As is commonly seen in AHR's, the nature of the base has a dramatic effect on the reaction (entries 6−10). The use of Et_3N resulted in a slower reaction but with enhanced selectivity. The

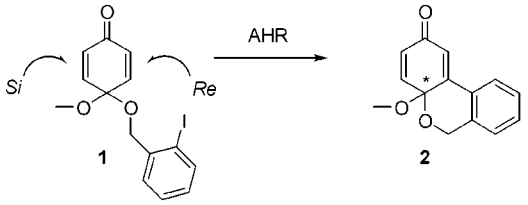


Figure 1. General asymmetric Heck reaction.

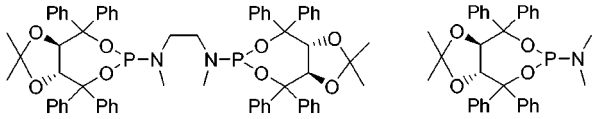
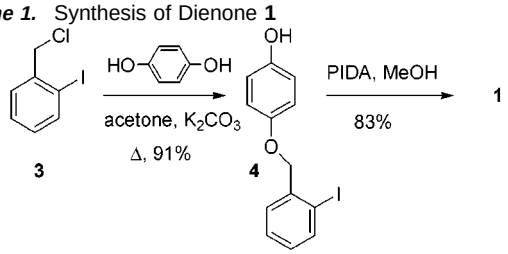


Figure 2. Chiral ligands used for the AHR.

Scheme 1. Synthesis of Dienone **1**



best results were obtained with iPr_2EtN and especially Cy_2MeN (based on recent reports of the effectiveness of this bulky tertiairy amine[15]), both with full conversion and high enantioselectivities of 89% and 90%, respectively. Additives such as nBu_4NX (X = I, OTf) or $iPr_2EtN{\cdot}HCl$ did not result in improvement of the reaction, whereas with silver salts no conversion was obtained. This AHR turned out not to be very sensitive to air and water and it could even be performed with nondistilled solvents.

Recent developments in asymmetric catalysis show that high enantioselectivities can be induced by monodentate chiral ligands,[6,16,17] and that monodentate BINOL based phosphoramidites are excellent ligands for rhodium-catalyzed asymmetric hydrogenations.[18] Although monodentate ligands were never very successful in inter- as well as intramolecular AHR's, we examined the monodentate analogue **L*-2**[19] of bidentate ligand **L*-1** in the Heck coupling of **1**.

Much to our delight the use of monodentate ligand **L*-2** resulted in a more selective conversion of **1** to **2** compared to the Heck coupling of **1** employing bidentate ligand **L*-2** (entries 15,16). Again Cy_2MeN is the base of choice. With use of $Pd(OAc)_2$ in the presence of **L*-2** and Cy_2MeN, full conversion was reached, providing **2** in 71% isolated yield with an excellent ee of 96%,[20,21] without the use of expensive silver or toxic thallium salts.

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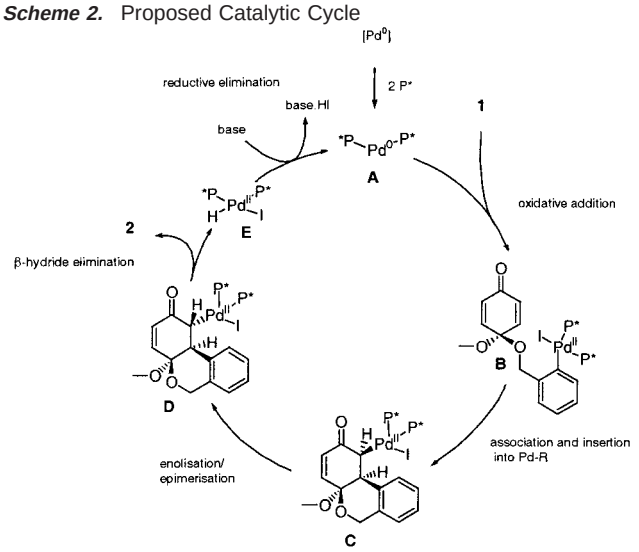
Table 1. AHR of **1** to **2**, Using Phosphoramidites as Ligand[a]

entry	L*	solvent	base	additive	conv. (%)[b]	ee (%)[c]
1	**L*-1**	THF	K_2CO_3		100	68
2	**L*-1**	CH_2Cl_2	K_2CO_3		100	84
3	**L*-1**	$CHCl_3$	K_2CO_3		100	86
4	**L*-1**	Toluene	K_2CO_3		100	80
5	**L*-1**	$CHCl_3$	PS[d]		<10	
6	**L*-1**	$CHCl_3$	K_3PO_4		60	86
7	**L*-1**	$CHCl_3$	PMP		68	87
8	**L*-1**	$CHCl_3$	Et_3N		35	92
9	**L*-1**	$CHCl_3$	*i*Pr_2EtN		100	89
10	**L*-1**	$CHCl_3$	Cy_2MeN		100	90
11	**L*-1**	$CHCl_3$	*i*Pr_2EtN	*i*Pr_2EtN·HCl	80	83
12	**L*-1**	$CHCl_3$	*i*Pr_2EtN	*e*	95	75
13	**L*-1**	$CHCl_3$	*i*Pr_2EtN	*f*	90	78
14	**L*-1**	$CHCl_3$	*i*Pr_2EtN	Ag_3PO_4	<2	
15	**L*-2**	$CHCl_3$	*i*Pr_2EtN		100	93
16	**L*-2**	$CHCl_3$	Cy_2MeN		100	96

[a] Reaction conditions: 0.3 mmol of dienone **1**, 6 mol % of $Pd(OAc)_2$, 12 mol % of ligand, 4 equiv of base, 3 mL of solvent, 1 equiv of additive, reflux, 2 days. [b] Determined by ^{1}H NMR, isolated yields at 100% conversion 70−75%. [c] Determined by HPLC analysis using a DAICEL OD or AS column. [d] Proton Sponge. [e] *n*Bu_4NI. [f] *n*Bu_4NOTf.

Scheme 2. Proposed Catalytic Cycle



For comparison, BINAP was also examined as a chiral ligand, using our optimized conditions or the Shibasaki[22] or Overman[23] conditions, and product **2** was obtained after 48 h in 0−50% yield and 0−5% ee.

On the basis of extensive mechanistic studies of Heck couplings, the formation of **2** can be rationalized as shown in Scheme 2. Initially, a chiral Pd(0) complex **A** is formed. Oxidative addition of dienone **1** results in Pd(II) complex **B**. Subsequent C−C bond formation (association and insertion into Pd−C) leads to complex **C**, which does not have a syn β-hydride. To reach the final product **2** epimerization of the C-2 center leading to **D** followed by syn β-hydride elimination to complex **E** needs to take place. The net trans elimination can be explained via a mechanism involving oxo-π-allylpalladium intermediates, similar to enolization in normal ketones,[11] which have found precedence in the Pd-catalyzed dehydrosilylation of silyl enolethers.[24] It should be noted that several examples of apparent trans β-hydride elimination have appeared in the literature.[25] Finally, reductive elimination of HI with base leads to the starting complex **A**. Preliminary mechanistic studies indicate a possible neutral pathway.[26,27]

In conclusion, an efficient enantioselective intramolecular Heck reaction of cyclohexadienones, using readily available and modular TADDOL-based mono- and bidentate phosphoramidites as chiral ligands and not requiring any additives, has been developed. Excellent enantioselectivities up to 96% ee are reached for the first time in a Heck reaction with monodentate ligands. Extension of the scope of this reaction and detailed mechanistic studies are currently in progress.

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Supporting Information Available: Experimental and chromatographic details (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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